Journal of Diabetes and Its Complications 33 (2019) 39–45

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Clinical features and long-term outcomes of diabetic kidney disease – A prospective cohort study from China

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ARTICLE INFO

Article history:
Received 9 July 2018
Received in revised form 15 August 2018
Accepted 26 September 2018
Available online 12 October 2018

Keywords:
Diabetic kidney disease
Proteinuric phenotype
Non-proteinuric phenotype
Clinical features
Outcomes

ABSTRACT

Background: Information regarding the clinical phenotypes of diabetic kidney disease (DKD) might guide better practice for clinicians. We aim to compare the clinical features and long-term outcomes of proteinuric and non-proteinuric phenotypes of DKD, based on a prospective cohort of Chinese population.
Methods: Altogether 8811 Chinese participants with diabetes were included. Kidney function decline was defined as estimated glomerular filtration rate <60 mL/min·1.73 m^{-2}. The presence of proteinuria by urine dipstick test was further divided into micro-proteinuria (trace or 1+) and overt-proteinuria (≥2+). Participants were then stratified into 5 groups: no DKD, isolated kidney function decline, isolated micro-proteinuria, isolated overt-proteinuria, and proteinuria combined with kidney function decline. Outcomes include the first occurrence of composite cardiovascular events, end-stage renal disease (ESRD), and all-cause mortality.
Main findings: After a median follow-up of 6.9 years, there were 646 composite cardiovascular events, 31 ESRD events, and 718 deaths. Isolated kidney function decline was only associated with the higher risk of ESRD (HRs 31.33 (95% CI 3.65–269.27)). Participants of overt-proteinuria and proteinuria combined with kidney function decline phenotypes were associated with increased risk of all predefined adverse outcomes.
Conclusions: Proteinuric and non-proteinuric DKD phenotypes might follow different pathophysiological pathways, and result in heterogeneous clinical features and prognosis.

1. Introduction

The expanding epidemic of diabetes worldwide has led to a concomitant rise in the prevalence of diabetes-related complications, in particular, diabetic kidney disease (DKD).[1,2] DKD is the leading cause of end-stage renal disease (ESRD), and it entails excess risk of morbidities as well as premature mortality.[3] Consequently, effective prevention and management of DKD are essential to attenuating the global burden of diabetes.

Micro-proteinuria (i.e. microalbuminuria) was previously considered as the clinical onset of DKD, and the decline of kidney function started only when overt-proteinuria (i.e. macroalbuminuria) occurred. However, emerging evidences have suggested that proteinuria does not always occur preceding the loss of renal function in diabetes, which contradicts the above-mentioned conventional paradigm of DKD.[4–6] As a specific phenotype, the non-proteinuric DKD has been increasingly recognized, particularly in those with type 2 diabetes.[1,7–10] Population-based studies from western countries have reported that about half of individuals with kidney function decline did not have preceding proteinuria or even never progressed to proteinuria in type 2 diabetes.[11] As compared with proteinuric DKD, non-proteinuric DKD revealed a weaker association with diabetic retinopathy.[12] These findings imply that patients with DKD could be further divided into different

Abbreviations: DKD, diabetic kidney disease; ESRD, end stage renal disease; FBG, fasting blood-glucose; CVD, cardiovascular disease; WC, waist circumference; BP, blood pressure; BMI, body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; GFR, glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiological Collaboration; CI, confidence intervals; HR, Hazard ratio.

Declarations of interest: None.

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https://doi.org/10.1016/j.jdiacomp.2018.09.019
1056-8727/

phenotypes according to the presence of proteinuria and/or the decline of kidney function.

To the best of our knowledge, studies on the comparison of clinical features and long-term outcomes of different phenotypes of DKD are insufficient. Recently, a large observational cohort study in Caucasians with type 1 diabetes found that non-albuminuric DKD was associated with an increased risk of cardiovascular morbidity and all-cause mortality to the same extent as albuminuric DKD.[4] Despite that it is more prevalent in type 2 diabetes, the outcomes of non-proteinuric DKD in patients with type 2 diabetes have only been reported in a few studies with relatively short follow-up, or retrospectively designed, which suggested a better prognosis of this phenotype when compared with proteinuric DKD.[8,13]

A significant epidemic of diabetes is present in Asian with a rapid increase in prevalence.[14,15] More than 60% of the world's population with diabetes came from Asia.[14,15] Epidemiological data have revealed that diabetes in Asian population has some characteristics different from the Caucasian. For example, individuals with diabetes in Asian were younger-onset, and were at a higher rate of clustering of other cardiovascular risk factors.[15] These discrepancies could inevitably influence the development, progression and prognosis of DKD. However, the current epidemiological data of comparison of clinical phenotypes of DKD are mainly from western countries, and due to the ethnical and environmental differences, the conclusions cannot be extrapolated to the Asian population. Therefore, our study aims to investigate the epidemiological and clinical features, as well as the long-term major adverse outcomes of proteinuric and non-proteinuric DKD phenotypes, based on a prospective cohort of Chinese population.

2. Methods

2.1. Study population

The current study was based on a diabetes subgroup from the Kailuan cohort, which was a prospective cohort study conducted in the community of Kailuan in Tangshan, a large industrial city located in Hebei province of China. The detailed study design and characteristics of the study population have been described previously.[16,17] Participants were predominantly patients with type 2 diabetes. Briefly, 101,510 employees aged 18 years or older (including the retired) in Kailuan group participated in the health examination and built their health records from June 2006 through October 2007. The participants underwent health examinations biennially. Items of examination included face-to-face questionnaire investigation, clinical examination and laboratory tests, which were conducted in Kailuan General Hospital and its ten affiliated hospitals.

We considered the 2008–2009 survey as the starting point and December 31, 2015 as the end of the follow up. The 2008–2009 survey was selected as the baseline in our study. Since this visit, the enzymatic method was used to measure serum creatinine (Scr). Firstly, we included participants who were diagnosed as diabetes according to the ADA 2010 criteria (fasting blood-glucose (FBG) ≥7.0 mmol/L, and/or self-reported history of diabetes and/or currently under blood glucose lowering therapy).[18] Secondly, we excluded people with a history of cardiovascular disease (CVD) or with maintenance dialysis ($N = 194$). Thirdly, we excluded individuals of age ≥85 years ($N = 36$), as well as missing data of clinical examination and laboratory tests in 2008–2009 survey ($N = 1817$). The detailed procedure of participant recruiting was shown in Fig. 1. Finally, a total of 8811 participants were included in the final analysis. Due to the concern of survival bias, individuals aged ≥85 years were excluded. This study was conducted according to the guidelines of Helsinki declaration and was approved by the ethics committee of Kailuan General Hospital and Peking University First Hospital. The informed contents were obtained from each participant before the health examination.

2.2. Data collection

During the on-site survey, all participants completed a questionnaire documenting their socio-demographic status (e.g., age, sex, and education), personal and family health history (e.g., hypertension, diabetes and CVD), and lifestyle habits. Anthropometric measurements such as height, weight, waist circumference (WC), and blood pressure (BP) were also collected. Height, weight and WC were measured according to the standard protocol. Height and WC were accurate to 0.1 cm and weight was accurate to 0.1 kg. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. BP was measured using a standardized mercury sphygmomanometer according to the standard procedures. Systolic BP and diastolic BP were taken at a 5-minute interval for two times after participants sitting for at least 5 min. The average of the two readings was used for further analysis. If the two measurements differed by >5 mm Hg, then a third measurement was conducted and the average of these three readings was used.

Serum samples were collected in the morning after an overnight fast and Scr, fasting blood glucose (FBG), lipids profile (including total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)) were tested using a Hitachi 7600 auto-analyzer (Hitachi; Tokyo, Japan). Scr was measured using the sarcosine oxidase assay method (Creatinine kit, BioSino Bio-technology and Science Inc., Beijing, China), with a lower limit detection of 22 μmol/L and an upper limit detection of 3000 μmol/L (linear correlation coefficient ≥ 0.99). Within laboratory intra- and inter-assay variable coefficients for serum creatinine were ≤5% and ≤6%, respectively. The estimated glomerular filtration rate (GFR) was calculated using the two-race Chronic Kidney Disease Epidemiological Collaboration (CKD-EPI) equation.[19] A single random midstream morning urine sample was collected from each participant. Urine protein concentration was assessed by the dry chemistry method with the test assay of H12-MA (Changchun Dirui Medical Technology Co., Ltd. Changchun, China). All the urine samples were measured using a urine analyzer (N-600, Dirui, Changchun, China) at the central laboratory of the Kailuan hospital. The levels of the semi-quantitative dipstick test were recorded as negative, trace, 1+, 2+, or 3+. We further defined micro-proteinuria (urine dipstick reading trace or 1+) and overt-proteinuria (urine dipstick reading ≥2+).[20]

2.3. DKD phenotypes

DKD was defined as diabetes with proteinuria, decline in kidney function (estimated GFR < 60 mL/min·1.73 m^{-2}), or both. We further defined four phenotypes of DKD according to the baseline status of estimated GFR and urinary dipstick tests: isolated kidney function decline (i.e. non-proteinuric DKD), isolated micro-proteinuria, isolated overt-proteinuria, and proteinuria combined with kidney function decline.

In our study, the semi-quantitative urine dipstick test was used for identifying proteinuria. Thus, we performed a validation study using 358 individuals who had the measures of urine dipstick and urine albuminuria creatinine ratio (ACR) simultaneously from the Kailuan study. The sensitivity and specificity of identified ACR ≥30 mg/g by urine dipstick ≥ trace were 57.1% and 88.9%, respectively. Participants fell into false-negative category were misclassified into the phenotypes of no DKD or isolated kidney function decline.

2.4. Other covariates

Hypertension was defined as a systolic BP ≥140 mm Hg or/and diastolic BP ≥90 mm Hg, or self-reported history of hypertension, or use of antihypertensive medication. Dyslipidemia was defined by the presence of at least one of the followings: serum TC level ≥ 200 mg/dL (5.2 mmol/L), TG ≥ 150 mg/dL (1.7 mmol/L), LDL-C ≥ 130 mg/dL (3.4 mmol/L), HDL-C < 40 mg/dL (1.0 mmol/L), and use of lipid-

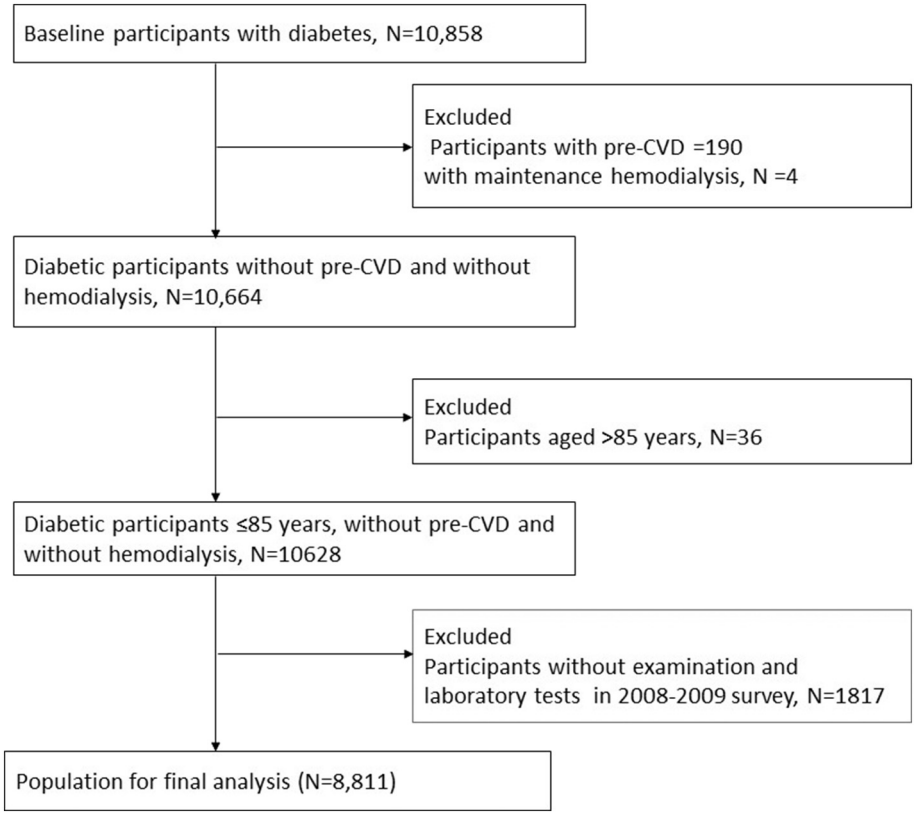

Fig. 1. Flow chart of the study participants.

lowering drugs.[21] Obesity was defined as BMI ≥28.0 kg/m^2 according to the recommendation by Working Group on Obesity in China.[22] Central obesity was defined as WC ≥90 cm and ≥80 cm for men and women, respectively.[23]

2.5. Assessment of outcomes

The major adverse outcomes included the first occurrence of composite cardiovascular (CV) events (non-fetal myocardial infarction (MI) and stroke (including ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage)), ESRD receiving hemodialysis, and all-cause mortality. Information on the composite CV events and ESRD receiving hemodialysis were collected from biennial personal interviews and medical records from medical insurance, and were further ascertained by the discharge summaries from the Kailuan General Hospital and its ten affiliated hospitals. It is worth noting that participants receiving medical service or hospitalization in other hospital could not get their health insurance reimbursement. This feature ensured that these major adverse outcomes would not be missed. Death information was collected from the provincial vital statistics office, discharge summaries, as well as medical records. The above outcomes were collected and recorded every 6 months. All outcomes were validated by the Data Safety Monitoring Board and the Arbitration Committee for Clinical Outcomes.

2.6. Statistical analysis

The baseline clinical features were described and compared among the four defined DKD phenotypes. Continuous data were presented as mean (standard deviation), categorical variables were presented as prevalence rate (with 95% confidence intervals [CI]). Moreover, the prevalence rate of four defined DKD phenotypes were reported according to age groups (<50 years; 50–65 years; and ≥65 years) and gender.

Furthermore, the incidence rate of major adverse outcomes was calculated and compared among different DKD phenotypes using the log-rank test. Incidence rates were expressed in cumulative incidences as well as person-years. Finally, the Cox proportional hazards model was used to determine the relationship between baseline DKD phenotypes and major adverse outcomes. Hazard ratio (HRs) with 95% CIs and *P*-values were reported. In the Cox model, the DKD phenotype variables were divided into 5 groups (no DKD, isolated kidney function decline, isolated micro-proteinuria, isolated overt-proteinuria, and proteinuria combined with kidney function decline). Four dummy variables were generated with the reference group as "no DKD". The proportional hazards assumption of the Cox regression model was verified by testing the interaction with time using the likelihood ratio test, which yielded non-significant *P*-values. The covariates included in the Cox regression model were age (10-year intervals, a continuous variable), male, family history of diabetes (defined as first-degree relatives suffered from diabetes through questionnaire), education level (high school and above versus below high school level), ever smoker, physical inactivity (defined as self-reported never or rarely exercise), hypertension (yes versus no), dyslipidemia (yes versus no), BMI status (<22 kg/m^2, 22–24 kg/m^2 (reference group), 24–28 kg/m^2, ≥28 kg/m^2), central obesity (yes versus no), FBG (a continuous variable), systolic BP (10-mm Hg intervals, a continuous variable), diastolic BP (10-mm Hg intervals, a continuous variable). All *P*-values were calculated from two-tailed tests of statistical significance, with type 1 error rate of 5%. All statistical analyses were performed using SAS 9.4 (SAS Institute; Cary, NC).

3. Results

3.1. Baseline characters of study population

Of the 8811 participants with diabetes (mean age 56.4 years, 83.3% male) involved in this study, a total of 2889 (32.8%) individuals were diagnosed as DKD. Among participants with DKD, 1445 (16.4%) were

micro-proteinuria, 504 (5.7%) were overt-proteinuria, and 1344 (15.3%) were presented with kidney function decline. Overall, the percentage of isolated kidney function decline (i.e. non-proteinuric DKD), isolated micro-proteinuria, isolated overt-proteinuria, and proteinuria combined renal impairment were 10.7%, 13.6%, 3.9% and 4.6%, respectively. The percentage of isolated kidney function decline (i.e. non-proteinuric DKD) increased with aging in both genders. Female patients were more vulnerable to isolated kidney function decline (i.e. non-proteinuric DKD), whereas males were more likely to have proteinuric DKD phenotype (Fig. 2).

3.2. Clinical features of proteinuric DKD and non-proteinuric DKD

The baseline clinical features of the study population (as a whole and stratified by different DKD phenotypes) were shown in Table 1. Compared with proteinuric DKD phenotypes, participants of isolated kidney function decline (i.e. non-proteinuric DKD) were substantially older, with lower levels of BP, FBG, as well as a relatively favorable metabolic profile (Table 1). The prevalences of certain metabolic disorders, such as dyslipidemia and obesity, were even lower than those participants without DKD. In comparison, participants with proteinuria, regardless of the presence of kidney function decline, have worse control of glycaemia and other metabolic disorders. In particular, participants of overt-proteinuria were presented with the highest levels of FBG, BP, TC and TG levels, and the most suboptimal metabolic profile among the four predefined DKD phenotypes (Table 1).

3.3. Cardiovascular-renal complications and all-cause mortality

After a median follow-up of 6.9 years (interquartile range 6.6–7.2), a total of 646 composite cardiovascular (CV) events occurred. In addition, 31 participants entered ESRD and received hemodialysis, and 718 participants died. Among the overall study population, the incidence of composite CV events, ESRD receiving hemodialysis and all-cause mortality were 1101.5, 51.1 and 1221.0 per 100,000 person-year, respectively (Table 2). Compared with participants without DKD, the predefined DKD phenotypes had significantly higher incidences of all adverse outcomes (*P*-values of log-rank test < 0.05), especially those of proteinuria combined with kidney function decline (Table 2). Among the four predefined DKD phenotypes, participants of isolated kidney function decline (i.e. non-proteinuric DKD) had the lowest incidence rate of composite CV events, whereas participants of isolated micro-proteinuria had the lowest incidence rate of ESRD receiving hemodialysis. Notably, participants of isolated overt-proteinuria had the highest incidence rate of MI.

3.4. Effects of different DKD phenotype on adverse outcomes

The results of multivariate Cox proportional hazards regression analysis were shown in Table 3. After adjusting for all covariates, isolated kidney function decline (i.e. non-proteinuric DKD) was only associated with excess risk of ESRD receiving hemodialysis (HR 31.33 (95% CI 3.65–269.27)), but not with higher risks of CV events and mortality. The phenotypes of isolated overt-proteinuria and proteinuria combined kidney function decline were both associated with excess risks of first occurrence of composite CV events (HR 1.53 (95% CI 1.11–2.11) and 1.48 (95% CI 1.09–2.00), respectively) and all-cause mortality (1.97 (95% CI 1.45–2.68), and 2.70 (95% CI 2.14–3.42), respectively). The micro-proteinuric phenotype was only associated with a higher risk of all-cause mortality (1.45 (95% CI 1.18–1.79)). Except for the isolated micro-proteinuria, the other three DKD phenotypes were associated with a significantly higher risk of ESRD receiving hemodialysis, with the lowest HRs for isolated kidney function decline (i.e. non-proteinuric DKD) and the highest HRs for proteinuria combined renal impairment.

4. Discussion

Using a large cohort of predominantly with type 2 diabetes, our study firstly presented the clinical features of DKD with proteinuria and without proteinuria in China, and further reported the long-term outcomes of DKD. Moreover, our study compared these adverse outcomes among different clinical phenotypes. Among participants of DKD, individuals of isolated kidney function decline (i.e. non-proteinuric DKD) demonstrated relatively benign prognosis, whereas individuals of isolated overt-proteinuric DKD revealed the highest CV risk, and individuals of both proteinuria and kidney function decline revealed the highest risk of ESRD event and mortality. Our findings improved the knowledge of clinical phenotypes of DKD in Asian, which might be valuable for a better understanding of the pathogenesis of developing different DKD phenotypes.

In our results, some differential features of proteinuric and non-proteinuric DKD were displayed. Individuals with isolated kidney function decline (i.e. non-proteinuric DKD) were substantially older, more likely to be female, consistent with previous studies.[7,24] Non-proteinuric phenotype revealed a relatively favorable metabolic profile in our findings, which had also been shown in some studies.[4,13] However, metabolic disorders were also suggested as potential risk factors of developing kidney function decline.[24] Possible reasons for the contradictory results might be the differences in population and study design. Compared with non-proteinuric DKD, individuals of proteinuric DKD phenotypes demonstrated poor control of blood glucose, BP, and lipid profile. In particular, individuals of isolated overt-proteinuric DKD

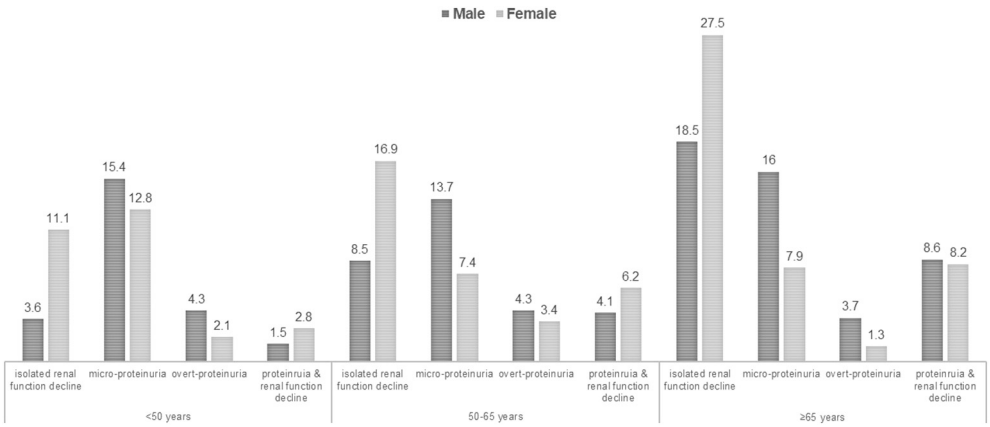

Fig. 2. The prevalence of four defined DKD phenotypes stratified by the gender and age. The percentage of non-proteinuric DKD increased with aging in both gender. Females have higher percentage of non-proteinuric DKD, and males have higher percentage of proteinuric DKD among different age groupings.

Table 1
Baseline clinical features of 8811 Chinese adults with diabetes stratified by the DKD phenotypes.

Characteristics	Overall	No DKD	DKD phenotypes			
			Isolated kidney function decline	Isolated micro-proteinuria	Isolated overt-proteinuria	Proteinuria combined with kidney function decline
Number	8811	5922	940	1200	345	404
Age (years)	56.4 (10.1)	55.3 (9.7)	61.7 (9.8)	56.0 (10.6)	56.1 (10.3)	61.9 (9.5)
Male (%)	83.3 (82.5–84.0)	83.9 (83.0–84.9)	71.9 (69.0–74.8)	89.5 (87.8–91.2)	88.4 (85.0–91.8)	78.5 (74.4–82.5)
Family history of diabetes (%)[a]	16.4 (15.6–17.2)	17.5 (16.5–18.5)	13.1 (10.9–15.2)	15.3 (13.3–17.4)	18.0 (13.9–22.0)	10.4 (7.4–13.4)
Education to high school or above (%)	15.1 (14.4–15.9)	15.4 (14.5–16.3)	14.0 (11.8–16.3)	16.3 (14.2–18.4)	13.4 (9.8–17.0)	11.1 (8.1–14.2)
Scr (μmol/L)	88.6 (33.8)	80.8 (17.1)	125.4 (61.7)	84.1 (17.2)	85.0 (17.5)	134.8 (66.0)
eGFR (mL/min·1.73 m^{-2})	82.4 (20.2)	88.7 (16.1)	51.8 (7.5)	86.2 (16.0)	85.0 (15.8)	49.3 (9.2)
FBG (mmol/L)	8.8 (3.5)	8.5 (3.4)	8.9 (3.5)	9.2 (3.5)	9.9 (3.2)	9.7 (3.8)
Systolic BP (mm Hg)	140 (21)	138 (20)	141 (21)	143 (21)	150 (24)	146 (23)
Diastolic BP (mm Hg)	87 (12)	87 (11)	85 (11)	90 (13)	92 (13)	88 (12)
BMI (kg/m^2)	26.1 (3.4)	26.0 (3.3)	25.9 (3.4)	26.2 (3.5)	27.0 (4.2)	26.4 (3.6)
WC (cm)	90.8 (10.2)	90.8 (10.2)	88.8 (9.7)	92.0 (10.4)	92.9 (11.3)	89.4 (10.6)
TC (mmol/L)	5.3 (1.5)	5.3 (1.4)	5.2 (2.0)	5.4 (1.2)	5.8 (2.9)	5.2 (1.1)
TG (mmol/L)	2.1 (2.5)	2.1 (2.6)	2.0 (1.8)	2.3 (2.5)	2.8 (3.4)	2.0 (1.4)
LDL-C (mmol/L)	2.8 (1.3)	2.7 (1.4)	2.8 (1.0)	2.9 (1.1)	2.9 (1.1)	2.8 (0.9)
HDL-C (mmol/L)	1.5 (0.5)	1.5 (0.5)	1.3 (0.4)	1.5 (0.4)	1.5 (0.5)	1.4 (0.3)
Hypertension (%)	58.0 (57.0–59.1)	54.5 (53.2–55.7)	57.9 (54.7–61.0)	65.5 (62.8–68.2)	75.1 (70.5–79.7)	73.0 (68.7–77.4)
Dyslipidemia (%)	70.1 (69.2–71.1)	69.4 (68.2–70.5)	68.7 (65.8–71.7)	73.1 (70.6–75.6)	76.8 (72.3–81.3)	69.3 (64.8–73.8)
Obesity (%)	25.7 (24.8–26.6)	24.8 (23.7–25.9)	24.6 (21.8–27.3)	27.0 (24.5–29.5)	36.5 (31.4–41.6)	27.5 (23.1–31.8)
Central obesity (%)	62.2 (61.1–63.2)	62.4 (61.2–63.7)	59.8 (56.6–63.0)	63.3 (60.5–66.0)	65.5 (60.5–70.5)	56.7 (51.8–61.5)
Ever smoker (%)	42.6 (41.6–43.7)	44.5 (43.2–45.7)	30.5 (27.6–33.5)	46.5 (43.7–49.4)	46.1 (40.8–51.3)	29.4 (25.0–33.9)
Physical inactivity (%)	77.4 (76.5–78.3)	77.4 (76.3–78.5)	69.1 (66.2–72.1)	81.7 (79.5–83.9)	84.3 (80.4–88.1)	77.4 (73.3–81.5)

Abbreviations: DKD, diabetic kidney disease; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; BMI, body mass index; WC, waist circumference; BP, blood pressure; UA, uric acid; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C high-density lipoprotein cholesterol.
Data are presented as means (standard deviation) or prevalence (95% confidential intervals).
[a] The family history of diabetes was defined as first-degree relatives suffered from diabetes through questionnaire.

presented the most suboptimal metabolic profile. Since these metabolic disorders were associated with adverse outcome in population with diabetes,[25] it can partially explain that participants of DKD have excess risks of developing adverse outcomes. Based on our findings, improvement of metabolic disorders might be helpful to delay the progression of DKD, especially in participants with proteinuric DKD phenotype. Further perspective studies are needed to clarify the relationship between metabolic disorders and DKD phenotypes.

Furthermore, we found that different DKD phenotypes were heterogeneous with respect to the risk of adverse outcomes. Based on our findings, overt-proteinuria was a robust predictor of CV risk, as well as an accelerated loss of kidney function and mortality, which is consistent with previous studies.[13,26] Therefore, primary prevention aiming to avoid the development of overt-proteinuria should be a priority. In contrast, participants with isolated micro-proteinuria were not associated with higher risks of CV and ESRD events. Previous studies have also showed that the predictive value of microalbuminuria in DKD progression remained controversial, and regression of microalbuminuria was observed in over 50% patients with diabetes.[5,27] Therefore, if the metabolic disorders were controlled well and RAS inhibitors were used timely at this stage, the progress of disease may be prevented or delayed. An increase of micro-proteinuria, especially progress to overt-

Table 2
Incidence rate of adverse outcomes stratified by the DKD phenotypes.

	Overall	No DKD	DKD phenotypes			
			Isolated kidney function decline	Isolated micro-proteinuria	Isolated overt-proteinuria	Proteinuria combined with kidney function decline
First occurrence of composite CV events						
Number of events	646	379	76	98	43	50
Cumulative incidence (95% CI)	7.3 (6.8–7.9)	6.4 (5.8–7.0)	8.1 (6.3–9.8)	8.2 (6.6–9.7)	12.5 (9.0–15.9)	12.4 (9.2–15.6)
Per 100,000 person-year	1101.5	951.8	1227.3	1241.7	1943.2	1976.6
MI						
Number of events	161	86	17	24	19	15
Cumulative incidence (95% CI)	1.8 (1.5–2.1)	1.5 (1.1–1.8)	1.8 (1.0–2.7)	2.0 (1.2–2.8)	5.5 (3.1–7.9)	3.7 (1.9–5.6)
Per 100,000 person-year	263.6	209.1	261.1	288.7	809.9	540.9
Stroke						
Number of events	508	301	62	76	29	40
Cumulative incidence (95% CI)	5.8 (5.3–6.3)	5.1 (4.5–5.6)	6.6 (5.0–8.2)	6.3 (5.0–7.7)	8.4 (5.5–11.3)	9.9 (7.0–12.8)
Per 100,000 person-year	847.3	743.9	967.9	935.4	1258.3	1507.5
ESRD receiving hemodialysis						
Number of events	31	1	6	2	6	16
Cumulative incidence (95% CI)	0.4 (0.3–0.5)	0.02 (0–0.05)	0.6 (0.1–1.1)	0.2 (0–0.4)	1.7 (0.4–3.1)	4.0 (2.1–5.9)
Per 100,000 person-year	51.1	2.4	93.7	24.3	256.1	602.2
All-cause mortality						
Number of events	718	354	100	122	47	95
Cumulative incidence (95% CI)	8.1 (7.6–8.7)	6.0 (5.4–6.6)	10.6 (8.7–12.6)	10.2 (8.5–11.9)	13.6 (10.0–17.2)	23.5 (19.4–27.7)
Per 100,000 person-year	1221.0	883.4	1626.4	1539.1	2123.3	3886.5

Data are n (%) unless stated otherwise. Abbreviations: CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; ESRD, end stage renal disease.

Table 3
Multivariate cox regression analysis for adverse outcomes.

Variables	Composite CV events		ESRD receiving hemodialysis		All-cause mortality	
	Hazard ratios (95% CI)	*P*-value	Hazard ratios (95% CI)	*P*-value	Hazard ratios (95% CI)	*P*-value
No DKD	1.00		1.00		1.00	
Isolated renal function decline	1.05 (0.81–1.35)	0.7115	31.33 (3.65–269.27)	0.0017	1.15 (0.91–1.44)	0.239
Isolated micro-proteinuria	1.12 (0.90–1.40)	0.3189	8.99 (0.81–99.79)	0.0737	1.45 (1.18–1.79)	0.0005
Isolated overt-proteinuria	1.53 (1.11–2.11)	0.0093	92.0 (10.86–787.52)	<0.0001	1.97 (1.45–2.68)	<0.0001
Proteinuria & kidney function decline	1.48 (1.09–2.00)	0.0111	267.15 (34.11–2092.39)	<0.0001	2.70 (2.14–3.42)	<0.0001

The data are presented as Hazard ratios (95% confidence intervals) and *P*-value. Models are adjusted for age, male, family history of diabetes, education level, smoking status, physical inactivity, hypertension, dyslipidemia, BMI status, central obesity, FBG, systolic BP, and diastolic BP.

proteinuria, portends a poor prognosis for CV and kidney outcomes. Therefore, in order to better target those high-risk patients, the regular assessment of proteinuria/albuminuria should be recommended.

Unlike proteinuric DKD, isolated kidney function decline (i.e. non-proteinuric DKD) was not associated with an increased risk of CV events and all-cause mortality. The better controlled metabolic disorders might partly account for the relatively better outcomes of this phenotype. Despite relatively benign, participants of this phenotype were associated with an over 30-fold increased risk of ESRD events during follow-up. As compared with proteinuric phenotypes of DKD, limited data on pathological features have shown that patients of isolated kidney function decline (i.e. non-proteinuric DKD) had more advanced tubulointerstitial and macroangiopathic lesions.[28] These pathological lesions were considered as determinants for long-term renal event,[28] which may partially explain our findings. Large longitudinal studies have shown an increasing prevalence of this phenotype during the past decades, and clinician should be aware of this phenotype.[10] Further studies are needed to explore the pathophysiological mechanism and treatment strategies of this phenotype.

Our study has some advantages, e.g. having a large sample size and a longitudinal design. Also, there are some limitations that are worth mentioning. Firstly, our data only have semi-quantitative urine dipstick, which has insufficiently sensitivity as compared with the urinary ACR. Since the sample size of participants without DKD was obviously larger than those of isolated kidney function decline phenotype, more participants with microalbuminuria could be misclassified into the former phenotype. Thus, the percentage of non-proteinuric DKD was unlikely to be significantly biased. In addition, despite mixed with a few participants with microalbuminuria, non-proteinuric DKD still revealed relatively benign prognosis among the four DKD phenotypes. Secondly, our study was based on a population with a majority of men and that may limit the generalizability of the study findings to women. Thirdly, the presence of proteinuria was not confirmed in repeated measurements during a short time period, e.g. 3–6 months. Fourthly, information regarding the causes of death was not available, which might lead to the underestimation of the incidence rate of CVD death and ESRD death, as well as affecting the estimated associations in the Cox regression model. Finally, people with impaired glucose tolerance, while with a normal fasting glucose level, would have been missed in the current analysis. This would cause a selection bias of the population.

5. Conclusions

Proteinuric and non-proteinuric DKD phenotypes might follow two different pathophysiological pathways, and result in heterogeneous clinical features and prognosis. Our findings provide important information that might guide better practice for clinicians in developing specific prevention and treatment strategies toward different DKD phenotypes.

Acknowledgements

Bixia Gao searched the literature, conceived and design the study, analysed the data, interpreted the results, and drafted the manuscript. Luxia Zhang and Min Chen organised and supervised the study, interpreted the results, and revised the manuscript. Kevin He made language editing of the manuscript. Minghui Zhao, Min Chen and Luxia Zhang obtained funding. Other members collected and analysed the data. Luxia Zhang and Min Chen are the guarantor and takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Funding

This study was supported by the grant from National Key Research and Development Program (No. 2016YFC1305405), the National Natural Science Foundation of China (No. 81641122) and Northern/Pacific Universities Global Health Research Training consortium of National Institutes of Health (No. R25 TW009345), a grant by the University of Michigan Health System and Peking University Health Sciences Center Joint Institute for Translational and Clinical Research (No. BMU20160466), and a grant by the interdisciplinary medicine Seed Fund of Peking University (No. BMU2018MX010). The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the manuscript for publication. No potential conflicts of interest relevant to this article were reported.

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